

REMARKS/ARGUMENTS

Status of the Claims:

Claims 1-64 were pending in the present application before this amendment as set forth above. Among them, claims 44-49 and 58-64 were under examination and claims 1-41 and 50-57 were withdrawn as being directed to non-elected subject matter. By this Amendment, claims 44 and 45 are amended.

The June 23, 2008 Office Action:

In the June 23, 2008 Office Action, the Primary Examiner objected to the disclosure because of informalities. The Examiner also rejected claim 45 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Further, claims 44-49 and 58-65 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,201,845 to Feder et al. (hereinafter "Feder").

Applicant very much appreciates the Primary Examiner's careful review of the application and would like to particularly thank Primary Examiner Ann Y. Lam and Supervisory Patent Examiner Mark L. Shibuya for granting and conducting a telephone interview held October 6, 2008 with Mr. Tim Xia and Mr. Christopher Glass, both Patent Attorneys for Applicant on the record, and Dr. John P. Wikswo, an Inventor. Applicant also thanks Primary Examiner Lam and Supervisory Patent Examiner Shibuya for their professionalism and patience shown during the telephone interview.

During the telephone interview, the June 23, 2008 Office Action was discussed. Among other things, Applicant submitted that in claims 44 and 45, the limitation of the bioreactor having a confining means with a first filter and second filter each "comprising a plurality of posts spaced apart from each other not to allow biological cells to pass through it" is not disclosed, taught, or suggested by the cited reference to Feder. The Primary Examiner then suggested that claim 44 be amended to recite each of the first filter and second filter as comprising *an array of posts* spaced apart from each other not to allow biological cells to pass through it, in order to differentiate the claimed invention from Feder. Moreover, the Primary Examiner acknowledged that Feder does not disclose a bioreactor wherein the chamber, inlet portion, first connection channel, outlet port,

and second connection channel are all formed in the first substrate such that, in operation, the stream of substance flows from the inlet port through the first connection channel, the chamber and the second connection channel to the outlet port in a direction that *is substantially parallel to the plane of the first surface of the first substrate*.

In response, as set forth above, claims 44 and 45 have been amended for better form. Specifically, claim 44 has been amended to recite an “array of posts” in the first filter and second filter of the confining means, as suggested by the Primary Examiner. Further, claim 45 has been amended to recite the stream of substance flowing in a direction “substantially parallel to the plane of the first surface of the first substrate.” In addition, the specification has been amended to correct informalities, so that the written description, claims, and drawings are consistent with each other.

Support for the amendments set forth above can be found in the disclosure as originally filed, and particularly, pages 18-27 of the specification and Figures 1-3 of the drawings.

Applicant submits that no new matter is added.

Any amendments to the claims not specifically referred to herein as being included for the purpose of distinguishing the claims from cited references are included for the purpose of clarification, consistence, and/or grammatical/spelling correction only.

It is now believed that the application is in condition for allowance and such allowance is respectfully requested.

The following remarks herein are considered to be responsive thereto.

Objections to the Disclosure

In the June 23, 2008 Office Action, the disclosure was objected to because of the following informalities: “paragraph 39 should be changed in the same manner as paragraph 108. That is, “outside” should be replaced by --inside--.” As set forth above, the replacement paragraph on page 11, lines 34-38 corrects these informalities. Support can be found in the disclosure as originally filed, for example, in Figs. 2A1, 2A2, and 2C of the drawings. It is now believed that the objection has been overcome.

Rejections under 35 U.S.C. § 112

In the June 23, 2008 Office Action, claim 45 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. With specific reference to the limitation “the plane of the first substrate” appearing in line 19 of claim 45, the Primary Examiner asserted that “[s]ince any object is a three dimensional object, and thus has more than one plane, it is not clear as to which plane of the first substrate Applicant refers [to].” In response, claim 45 has been amended to read, in part, “...in a direction that is substantially parallel to the plane of the *first surface of the* first substrate.” (Emphasis added.) Support for this amendment can be found in the disclosure as originally filed, for example in Fig. 2A1. It is now believed that this rejection has been overcome.

Rejections under 35 U.S.C. §103

In the June 23, 2008 Office Action, claims 44-49 and 58-65 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Feder. Applicant respectfully traverses these rejections for at least the following reasons:

Claim 44:

Among other unique limitations, independent claim 44, as amended, recites a “bioreactor comprising:

- i) a first substrate having a first surface and an opposite second surface, defining a chamber therebetween the first surface and the opposite second surface of the first substrate for receiving biological cells and a liquid medium;
- ii) an inlet port formed in the first substrate and apart from the chamber;
- iii) a first connection channel formed in the first substrate, wherein the first connection channel is in fluid communication with the inlet port and the chamber for allowing a stream of substance to be delivered to the chamber;
- iv) an outlet port formed in the first substrate and apart from the chamber;
- v) a second connection channel formed in the first substrate, wherein the second connection channel is in fluid communication with the outlet port and the chamber for allowing a stream of substance to be removed from the chamber; and
- vi) confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium,

wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate;

wherein the confining means comprises a *first filter and a second filter*, wherein the first filter is positioned proximate to the first connection channel and the second filter is positioned proximate to the second connection channel, and the first filter and the second filter are substantially parallel to each other; and wherein *each of the first filter and the second filter comprises an array of posts spaced apart from each other not to allow biological cells to pass through it.*" (Emphasis added.)

As described in the specification as originally filed, for example, in paragraphs on page 23, lines 17-38 to lines 1-10 on page 26 and shown in Figs. 2A1, 2A2, and 2C of the drawings, the bioreactor 1000 has a chamber 1006, first connection channel 1021, second connection channel 1005, inlet port 1021, and outlet port 1005, which are *all formed in the first substrate 1001*. Moreover, as shown in Figs. 2A1 and 2C, the confining means 1003 "includes a *first filter 1085a* and a *second filter 1085b*, where the first filter 1085a is positioned proximate to the first connection channel 1021 and the second filter 1085b is positioned proximate to the second connection channel 1005, and the first filter 1085a and the second filter 1085b are substantially parallel to each other." (Emphasis added.) Also, as shown *each of the first filter 1085a and the second filter 1085b comprises an array of posts 1086 spaced apart from each other not to allow cells to pass through it.*

In contrast, Feder discloses a *macroscopic* device, which is assembled in multiple layers requiring fastening together with bolts and nuts and pipe. As shown in Figs. 2 and 3, bolts 37 are used for connecting the *separate, detachably joined parts* of the upper part of the housing 13 with the lower part of the housing 12. With specific regard to the Primary Examiner's assertion that "[P]art (12) is equivalent to applicant's claimed first substrate," Applicant respectfully submits that in Feder, the *cells grow on the hollow fibers that are contained within the chamber*, and hence, Feder's part 12 is clearly not equivalent to the first substrate of the present invention.

With regard to integration of parts, it is submitted that in MPEP 2144.04, citing *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (Claims were directed to a vibratory testing machine (a hard-bearing wheel balancer) comprising a holding structure, a base structure, and a supporting means which form "a single integral and gaplessly continuous piece." Nortron argued that the invention is just making integral what had been made in four bolted

pieces. The court found this argument unpersuasive and held that the claims were patentable because the prior art perceived a need for mechanisms to dampen resonance, whereas the inventor eliminated the need for dampening via the one-piece gapless support structure, showing insight that was contrary to the understandings and expectations of the art.)

Therefore, Applicant respectfully submits that Feder does not disclose, teach, or suggest a bioreactor having "...confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium, *wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate*" as recited in amended claim 44 of the present invention. (Emphasis added.)

Moreover, Applicant respectfully submits that Feder does not disclose, teach, or suggest a bioreactor wherein "the confining means comprises a *first filter and a second filter*,...and wherein *each of the first filter and the second filter comprises an array of posts spaced apart from each other not to allow biological cells to pass through it*," and having all the other limitations of amended claim 44 of the present invention. (Emphasis added.)

Thus, Applicant respectfully submits that Feder simply does not disclose, teach, or suggest a bioreactor having *all* the limitations as recited in amended claim 44. For at least these reasons, previously presented independent claim 44 is patentable under 35 U.S.C. §103(a) over Feder.

Accordingly, claims 46-49, which depend from allowable independent claim 44, as amended, are also allowable for at least this reason.

Claim 45:

Among other unique limitations, claim 45, as amended, recites a bioreactor comprising:

- i) a first substrate having a first surface and an opposite second surface, defining a chamber therebetween the first surface and the opposite second surface of the first substrate for receiving biological cells and a liquid medium;
- ii) an inlet port formed in the first substrate and apart from the chamber;
- iii) a first connection channel formed in the first substrate, wherein the first connection channel is in fluid communication with the inlet port and the chamber for allowing a stream of substance to be delivered to the chamber;

- iv) an outlet port formed in the first substrate and apart from the chamber;
- v) a second connection channel formed in the first substrate, wherein the second connection channel is in fluid communication with the outlet port and the chamber for allowing a stream of substance to be removed from the chamber; and
- vi) confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium, ***wherein the confining means comprises an array of posts,*** wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate such that, ***in operation, the stream of substance flows from the inlet port through the first connection channel, the chamber and the second connection channel to the outlet port in a direction that is substantially parallel to the plane of the first surface of the first substrate;*** and wherein the first substrate further defines a first alternate port and a third connection channel in fluid communication with the first alternate port and the confined region of the chamber for allowing seed biological cells to perfuse only inside the confined region in the chamber. (Emphasis added.)

As shown in Figs. 2A1-2I of the drawings as originally filed and described in the specification as originally filed, for example, in paragraphs on line 28-38 of page 18 and lines 7-18 of page 19, the bioreactor according to one embodiment of the present invention is a ***microfluidic*** device which integrates “suitable cell culture and microfabrication techniques to permit cell growth in ***small, confined, well perfused volumes*** at tissue densities, ***provide[s] independent control of*** multiple chemokines and growth factor gradients, ***shear forces, tissue perfusion,*** and permeability of physical barriers to cellular migration, and allow[s] detailed optical and electrochemical observation of normal and cancerous cells during cell migration, intravasation, extravasation, angiogenesis, and other cellular processes.” (Emphasis added.)

In contrast, the disclosure of Feder is directed specifically at a class of bioreactor that is radically different from the present invention as claimed in amended claim 45. For instance, Feder discloses that “[i]n accordance with the present invention, cell culture apparatus for the growth of cells in vitro is provided ***which employs elongate, selectively permeable hollow fibers*** in a shallow layer configuration as a matrix for cell attachment on the outer surface of the fibers,

and aeration of the cells by passage through the interior of said fibers and permeation of the membrane wall.” Feder, Col. 2, lines 22-28.

In operation of Feder’s device, “cell culture medium is *fed into chamber 23 through inlet ports 26 and 27*. The medium is inoculated through port 29 with a seed culture During the incubation, periodic changes of media can be made, with the spent medium *being expelled through outlet port 28* and fresh medium again being supplied through inlet ports 26 and 27. Samples of macromolecular materials can be *withdrawn through access port 29* at any desired time during the incubation. *The culture medium flows into the lower part of chamber 23 beneath perforated plate 35 which thereby serves as manifold or distributor means* to provide uniform distribution of the medium and *a flow path which is upward and transverse to the plane of the elongate axes of the fibers*.” (Feder, col. 4, lines 56-68 through col. 5, lines 1-29, and Figs. 2 and 3) (Emphasis added.) In other words, in Feder’s device, the culture medium *flows from the inlet ports 26 and 27, through the perforated plate 35 (or filter plate 40, Fig. 4) into the fiber layer 34, and then is expelled through outlet port 28, i.e., the flow of the culture medium is transverse to the planar region containing the cells*, i.e. the bed of parallel hollow fibers.

Thus, Feder does not disclose, teach, or suggest a bioreactor “wherein the chamber, the inlet portion, the first connection channel, the outlet port, and the second connection channel are all formed in the first substrate such that, *in operation, the stream of substance flows from the inlet port through the first connection channel, the chamber and the second connection channel to the outlet port in a direction that is substantially parallel to the plane of the first surface of the first substrate*,” and having all of the other limitations recited in amended claim 45 of the present invention.

In addition, referring to and incorporating herewith the reasons set forth above why amended claim 44 is patentable under 35 U.S.C. § 103 over Feder, Applicant respectfully submits that independent claim 45, as amended, is patentable for at least these reasons, as well. Specifically, Feder does not disclose, teach, or suggest a bioreactor having “confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium, *wherein the confining means comprises an array of posts*” and having all of the other limitations recited in amended claim 45 of the present invention.

Therefore, Feder does not disclose, teach, or suggest a bioreactor having all of the limitations as recited in amended claim 45 of the present invention. For at least these reasons, amended claim 45 is patentable under 35 U.S.C. §103(a) over Feder.

Accordingly, previously presented claims 58-65, which depend from now allowable amended claim 45, are also allowable for at least this reason.


CONCLUSION

Applicant respectfully submits that the foregoing Amendment and Response place this application in condition for allowance. If the Primary Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Primary Examiner's amendment, please call the undersigned at 404.495.3678. The Commissioner is hereby authorized to charge any petition fee under 37 CFR 1.17(f), (g) or (h) or any deficiency of fees and credit of any overpayments to Deposit Account No. 50-3537.

Respectfully submitted,

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